UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/948,149	10/09/97	FENDLY B	P1053R2

HM12/0710

WENDY M LEE
GENENTECH INCORPORATED
1 DNA WAY
SOUTH SAN FRANCISCO CA 94080

EXAMINER	
SWARTZ,R	
ART UNIT	**PAPER NUMBER**
1645	20

DATE MAILED: 07/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/948,149	Fendly et al
Examiner	**Group Art Unit**
Rodney P. Swartz, Ph.D.	1641

☒ Responsive to communication(s) filed on *17May2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *28-40 and 42-58* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *28-40 and 42-58* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *19*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Please note that the Art Unit of your application in the PTO has changed to Art Unit 1645.

Continued Prosecution Application

2. The request filed on 17May2000 for a Continued Prosecution Application (CPA) under 37 CAR 1.53(d) based on parent Application No. 08/948,149 is acceptable and a CPA has been established. An action on the CPA follows.

3. Applicants' Amendment, received 17December1999, paper#13, is acknowledged and has been entered. New claims 56-58 have been added.

4. Currently, claim 28-40 and 42-58 are under consideration.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

7. Claims 28-31, 37-38, 40, and 56, and 57 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shepard et al (*J. Clin. Immunol.*, 11(3):117-127, 1991).

The instant claims utilize the open language "comprising" in delineating the methods steps. Such language encompasses induction of apoptosis which is taught in the instant specification as one of the mechanisms by which the claimed antibodies induce cell death, but the scope of the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other reagents, such as complement, phagocytic cells, cytotoxic drugs, or growth inhibitory agents, in addition to the antibodies. The specification teaches that antibodies 7C2 and 7F3 bind to Domain of ErbB2 and that antibody 4D5 binds to ErbB2 but not to Domain 1.

Shepard et al teach a monoclonal anti-HER2 antibody (4D5) which: a) inhibits the growth of SKBR3 breast tumor cells in cell culture by 66% (Abstract; Table II); b) enhances the sensitivity of SKBR3 cells to cisplatin (Figure 5); and c) enhances the sensitivity of SKBR3 cells to TNFα (Figure 4). Shepard et al also teach monoclonal anti-HER2 antibodies 7C2 and 7F3

which bind to Domain 1 of ErbB2 (Figure 2; page 119, section **Derivation of muMab 4D5**) and which inhibit SKBR3 proliferation by 21% and 38% respectively (Table II).

In the absence of evidence to the contrary, antibodies 7C2, 7F3, and 4D5 in the instant application are the same antibodies in the cited references because applicant Brian M. Fendly, of Genentech, Inc., is also the co-author on both cited references, which also list Genentech, Inc. as the address of correspondence. Both the instant application and the cited references also teach that the antibodies bind to ErbB2. Therefore, the antibodies are the same because: 1) same laboratory, 2) same author/applicant, 3) same laboratory designation for the antibodies, 4) same procedures for producing antibodies, and 5) same reactivity, i.e., bind to ErbB2(HER2).

Since the **same laboratory designation** is utilized in both the instant application and the cited references, **from the same laboratory**, the properties of antibodies 7C2, 7F3 and 4D5 in the cited references are inherent concerning: 1) binding to Domain 1 of ErbB2, 2) binding another Domain, and 3) 5-50 fold induction of annexin binding.

8. Claims 28-31, 37-38 and 40 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lewis et al (*Cancer Immunol. Immunother.*, 37:255-263, 1993).

The instant claims utilize the open language "comprising" in delineating the methods steps. Such language encompasses induction of apoptosis which is taught in the instant specification as one of the mechanisms by which the claimed antibodies induce cell death, but the scope of the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other

reagents, such as complement, phagocytic cells, cytotoxic drugs, or growth inhibitory agents, in addition to the antibodies. The specification teaches that antibodies 7C2 and 7F3 bind to Domain of ErbB2 and that antibody 4D5 binds to ErbB2 but not to Domain 1.

Lewis et al teach monoclonal anti-HER2 monoclonal antibodies, e.g., 4D5, 7C2, and 7F3, which inhibit human tumor cells such as SKBR3 (Table 2) and mediate antibody-dependent cellular cytotoxicity (Figure 4).

In the absence of evidence to the contrary, antibodies 7C2, 7F3, and 4D5 in the instant application are the same antibodies in the cited references because applicant Brian M. Fendly, of Genentech, Inc., is also the co-author on both cited references, which also list Genentech, Inc. as the address of correspondence. Both the instant application and the cited references also teach that the antibodies bind to ErbB2. Therefore, the antibodies are the same because: 1) same laboratory, 2) same author/applicant, 3) same laboratory designation for the antibodies, 4) same procedures for producing antibodies, and 5) same reactivity, i.e., bind to ErbB2(HER2).

Since the **same laboratory designation** is utilized in both the instant application and the cited references, **from the same laboratory**, the properties of antibodies 7C2, 7F3 and 4D5 in the cited references are inherent concerning: 1) binding to Domain 1 of ErbB2, 2) binding another Domain, and 3) 5-50 fold induction of annexin binding.

9. Claims 32-36, 39, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable Shepard et al (*J. Clin. Immunol.*, 11(3):117-127, 1991), or Lewis et al (*Cancer Immunol. Immunother.*, 37:255-263, 1993), in view of Fendly et al (*Cancer Research*, 50:1550-1558,

1990), Deshane et al (*J. Invest. Med.*, 43(Suppl 2):328A, 1995), and further in view of Senter et al (U.S. Pat. No. 4,975,278).

The instant claims utilize the open language "comprising" in delineating the methods steps. Such language encompasses induction of apoptosis which is taught in the instant specification as one of the mechanisms by which the claimed antibodies induce cell death, but the scope of the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other reagents, such as complement, phagocytic cells, cytotoxic drugs, or growth inhibitory agents, in addition to the antibodies. The specification teaches that antibodies 7C2 and 7F3 bind to Domain of ErbB2 and that antibody 4D5 binds to ErbB2 but not to Domain 1.

Shepard et al teach a monoclonal anti-HER2 antibody (4D5) which: a) inhibits the growth of SKBR3 breast tumor cells in cell culture by 66% (Abstract; Table II); b) enhances the sensitivity of SKBR3 cells to cisplatin (Figure 5); and c) enhances the sensitivity of SKBR3 cells to TNFα (Figure 4). Shepard et al also teach monoclonal anti-HER2 antibodies 7C2 and 7F3 which bind to Domain 1 of ErbB2 (Figure 2; page 119, section **Derivation of muMab 4D5**) and which inhibit SKBR3 proliferation by 21% and 38% respectively (Table II).

Lewis et al also teach monoclonal anti-HER2 monoclonal antibodies, e.g., 4D5, 7C2, and 7F3, which inhibit human tumor cells (Table 2) and mediate antibody-dependent cellular cytotoxicity (Figure 4).

Fendly et al teach the production and characterization of the monoclonal anti-HER2 antibodies utilized by Shepard et al and Lewis et al (Abstract; page 1550-1552, section **Materials and Methods**).

Deshane et al teach that intracellular antibody knockout of the ErbB2 oncoprotein achieves targeted eradication of tumor targets by induction of apoptosis.

Senter et al teach a method for delivery of cytotoxic drugs to tumor cells by using a tumor specific antibody/enzyme conjugate that binds to the tumor cells, and upon additional administration of a prodrug, the enzyme converts the prodrug to an active cytoxic drug (Abstract; Figure 1; column 4, line 5 to column 5, line 4).

Thus, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to use the monoclonal anti-HER2 monoclonal antibodies, such as 4D5, 7C2, and 7F3, as taught by Shepard et al, Lewis et al, and Fendly et al to induce cell death in cells overexpressing ErbB2 receptor by a variety of methods, one of which is apoptosis. Likewise, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to enhance the efficacy of the monoclonal antibodies by using the reagents and techniques taught by Senter et al, or by using in concert with the monoclonal antibody treatment, radiation treatments as widely used in the treatment of tumors.

10. Claims 42-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shepard et al (*J. Clin. Immunol.*, 11(3):117-127, 1991), in view of Lewis et al (*Cancer Immunol.*

Immunother., 37:255-263, 1993) and Fendly et al (*Cancer Research*, 50:1550-1558, 1990), and further in view of Deshane et al (*J. Invest. Med.*, 43(Suppl 2):328A, 1995) and Senter et al (U.S. Pat. No. 4,975,278).

The instant claims utilize the open language "comprising" in delineating the methods steps. Such language encompasses induction of apoptosis which is taught in the instant specification as one of the mechanisms by which the claimed antibodies induce cell death, but the scope of the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other reagents, such as complement, phagocytic cells, cytotoxic drugs, or growth inhibitory agents, in addition to the antibodies. The specification teaches that antibodies 7C2 and 7F3 bind to Domain of ErbB2 and that antibody 4D5 binds to ErbB2 but not to Domain 1.

In the absence of evidence to the contrary, antibodies 7C2, 7F3, and 4D5 in the instant application are the same antibodies in the cited references, Shepard et al, Lewis et al, and Fendly et al, because applicant Brian M. Fendly, of Genentech, Inc., is also the co-author on these cited references, which also list Genentech, Inc. as the address of correspondence. Both the instant application and the cited references also teach that the antibodies bind to ErbB2. Therefore, the antibodies are the same because: 1) same laboratory, 2) same author/applicant, 3) same laboratory designation for the antibodies, 4) same procedures for producing antibodies, and 5) same reactivity, i.e., bind to ErbB2(HER2).

Lewis et al also teach monoclonal anti-HER2 monoclonal antibodies, e.g., 4D5, 7C2, and 7F3, which inhibit human tumor cells (Table 2) and mediate antibody-dependent cellular

cytotoxicity (Figure 4). While Lewis et al do not teach that antibodies 7C2 and 7F3 bind to Domain 1 of ErbB2, the antibodies taught by Lewis et al would bind to Domain 1 of ErbB2, as these antibodies the same as those of the instant application, in the absence of evidence to the contrary (see discussion above). Lewis et al do not teach *in vivo* administration of the antibodies, but do suggest that these antibodies will add to the repertoire of therapeutic agents directed against human cancers characterized by amplification of the HER2 protooncogene (page 262, end of column 1). While Lewis et al do teach exposing a tumor cell to an antibody which does not bind to Domain 1 of ErbB2 (4D5), Lewis et al do not teach such exposure in conjunction with another antibody. Lewis et al do not teach that cell death is induced by apoptosis.

Shepard et al teach a monoclonal anti-HER2 antibody (4D5) which: a) inhibits the growth of SKBR3 breast tumor cells in cell culture by 66% (Abstract; Table II); b) enhances the sensitivity of SKBR3 cells to cisplatin (Figure 5); and c) enhances the sensitivity of SKBR3 cells to TNFα (Figure 4). Shepard et al also teach monoclonal anti-HER2 antibodies 7C2 and 7F3 which bind to Domain 1 of ErbB2 (Figure 2; page 119, section **Derivation of muMab 4D5**) and which inhibit SKBR3 proliferation by 21% and 38% respectively (Table II). Shepard et al teach a **nude mouse model** wherein the antibody localizes at the tumor site and **inhibits growth of human** tumor xenografts which over express HER2(ErbB2) (section ***In vivo* Preclinical Efficacy**, page 122-123). Shepard et al suggest, that based upon such *in vivo* data, over expression of the protein in human cancer makes this receptor an attractive target for development of cancer therapeutics (page 126, lines 5-8). Shepard et al does not teach exposing

a tumor cell to more than one antibody at a time. Shepard et al do not teach that cell death is induced by apoptosis.

Fendly et al is cited to teach the production and characterization of the monoclonal anti-HER2 antibodies utilized by Shepard et al and Lewis et al (Abstract; page 1550-1552, section **Materials and Methods**).

Deshane et al is cited to teach that intracellular antibody knockout of the ErbB2 oncoprotein (to which the antibodies 4D5, 7C2, and 7F3 bind) achieves targeted eradication of tumor targets by induction of apoptosis.

Senter et al is cited to teach methods of chemotherapeutic agent delivery to tumor cells by using tumor specific antibody/enzyme conjugates that bind to tumor cells. Upon additional administration of a prodrug, the enzyme converts the prodrug into an active chemotherapeutic agent (Abstract; Figure 1, column 4, line 5 to column 5, line 4).

Thus, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to use the monoclonal anti-HER2 monoclonal antibodies, such as 4D5, 7C2, and 7F3, as taught by Shepard et al, Lewis et al, and Fendly et al to induce cell death in cells over expressing ErbB2 receptor, either by utilizing the antibodies individually, or to maximize efficacy, utilizing combinations of the antibodies. Likewise, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to enhance the efficacy of the monoclonal antibodies by using the chemotherapeutic agents and techniques taught by Senter

et al, or by using in concert with the monoclonal antibody treatment, radiation treatments as widely used in the treatment of tumors.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rodney P. Swartz, Ph.D., whose telephone number is (703) 308-4244. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM EST.

If attempts to reach the Examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F. Smith, can be reached on (703)308-3909. The facsimile telephone number for the Art Unit Group is (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703)308-0196.

RODNEY P. SWARTZ, PH.D
PRIMARY EXAMINER
Art Unit 1645

July 7, 2000